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Anti-Markovnikov Hydroamination of Alkenes Catalyzed by an Organic Photoredox System

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Supporting Information

ABSTRACT: Herein we report a metal-free method for the direct anti-Markovnikov hydroamination of unsaturated amines. Irradiation of the amine substrates with visible light in the presence of catalytic quantities of easily synthesized 9-mesityl-10-methylacridinium tetrafluoroborate and thiophenol as a hydrogen-atom donor furnished the nitrogen-containing heterocycles with complete regiocontrol. Two examples of intermolecular anti-Markovnikov alkene hydroamination are also disclosed.

The direct addition of N−H across an alkene[1] provides an efficient, atom-economical route to highly valuable, biologically active nitrogen-containing compounds.[2] Considerable effort has been devoted to the development of catalyst systems for alkene hydroamination, with the majority of these strategies exhibiting preferential Markovnikov selectivity.[3,4] Thus, accessing anti-Markovnikov reactivity has proven quite challenging, and considerably fewer reports exist in this arena. Catalytic intermolecular anti-Markovnikov olefin hydroamination reactions have been demonstrated using transition metals,[5] alkaline-earth metals,[5l,5] and, to a limited extent, photosensitizers.[6,7]To our knowledge, the only intramolecular anti-Markovnikov hydroamination of styrenes, which employs a Rh catalyst at elevated temperatures (eq 1 in Figure 1), was reported by the Hartwig group in 2006.[8,9] Recently, our group reported an anti-Markovnikov hydroalkoxylation reaction using a photocatalyst/H-atom donor system.[10] Given the paucity of intramolecular anti-Markovnikov hydroamination reports, we saw an opportunity to demonstrate the utility of our catalytic strategy toward this end. Herein we report a metal-free anti-Markovnikov hydroamination of unsaturated amines using 9-mesityl-10-methylacridinium tetrafluoroborate (**A**) as the catalyst and thiophenol as the H-atom donor (eq 2 in Figure 1).

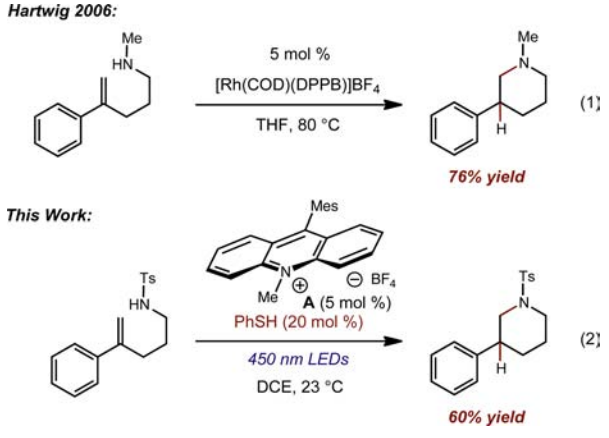

Figure 1. Catalytic anti-Markovnikov intramolecular hydroaminations.

In our previously reported hydroalkoxylation reaction, we took advantage of the well-documented single-electron oxidation of alkenes to provide unique radical cations that give rise to anti-Markovnikov reactivity.[11−13] We proposed to apply this strategy to the hydroamination reaction, although we anticipated some challenges associated with amine oxidation.[14] Sufficiently electron-rich amines are susceptible to oxidation at nitrogen, and numerous groups have taken advantage of this reactivity.[15]While this pathway could lead to productive hydroamination, it could also result in undesirable side reactions stemming from amine radical cation intermediates. Judicious selection of the amine protecting group could circumvent these potential issues, and for this reason, we elected first to examine the use of a sulfonyl group, as it should be adequately electron-withdrawing to suppress amine oxidation yet still render the amine nucleophilic.

We began our studies by submitting *p*-toluenesulfonyl-protected isoprenylamine **9a** to our previously reported conditions for the anti-Markovnikov hydroalkoxylation reaction. Despite the low yield obtained (16%), complete anti-Markovnikov regioselection (>20:1) was observed in the formation of the desired pyrrolidine product after 3 days (Table 1, entry 1). After additional efforts at reaction optimization (solvent, addition of organic and inorganic bases, concentration, etc.) failed to increase the reaction efficiency, we turned our attention to the identity of the H-atom donor. While 9-cyanofluorene (entry 2) gave essentially the same result as did phenylmalononitrile, the heteroatomic hydrogen donor thiophenol provided a 2-fold increase in the yield (entry 3).[16] When the thiophenol loading was decreased to 20 mol %, we were pleased to find that pyrrolidine **9b** could be obtained in 70% yield as a single regioisomer (entry 4). To our knowledge, this result represents a rare example of an intramolecular anti-Markovnikov hydroamination of a non-activated olefin.[3b,4a]

Control experiments revealed that thiophenol, light, and photocatalyst were all necessary for productive reactivity (entries 8−10). The use of thiophenol as the H-atom donor allowed us to explore the use of alternative common protecting groups for amines. While a benzyl protecting group afforded

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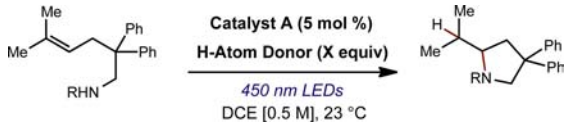
Table 1. Optimization Studies[a]



Entry	R	H-Atom Donor	Time	Yield[b]
1	Ts	1.0 equiv of $PhCH(CN)_2$	72 h	16%
2	Ts	1.0 equiv of 9-cyanofluorene	72 h	12%
3	Ts	1.0 equiv of PhSH	72 h	41%
4	Ts	0.2 equiv of PhSH	96 h	70%[c]
5	H	0.2 equiv of PhSH	96 h	<5%
6	Bn	0.2 equiv of PhSH	96 h	15%
7	Boc	0.2 equiv of PhSH	96 h	65%
8	Ts	none	96 h	<5%
9	Ts	0.2 equiv of PhSH without photocatalyst	24 h	<5%
10	Ts	0.2 equiv of PhSH without light	24 h	<5%

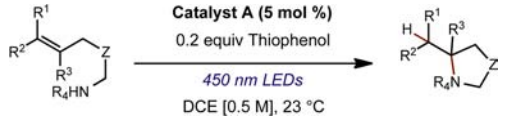
[a]Irradiation was performed with a 15 W, 450 nm light-emitting diode (LED) flood lamp. [b]Determined by ^{1}H NMR analysis. [c]Isolated yield.

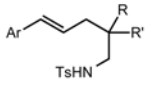
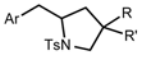
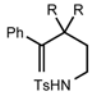
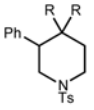
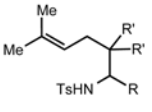
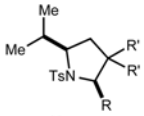
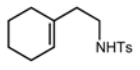
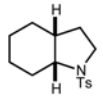
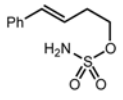
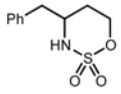
only a small amount of the pyrrolidine adduct (15% yield; entry 6), presumably because of the formation of numerous unidentified side products, we found that the Boc protecting group was suitable in this context (65% yield; entry 7). This supported our hypothesis that electron-rich amines would be poor substrates because of their susceptibility to oxidation. While the use of a Boc protecting group was quite appealing because of its ease of removal, we elected to evaluate tosylamine substrates because of their straightforward characterization.

We next shifted our focus to investigate the scope of the alkene hydroamination reaction (Table 2). Amine substrates bearing pendant styrenes underwent smooth 5-exo cyclization to furnish the corresponding regioisomerically pure pyrrolidines (entries 1−6). It should be noted that similar reactivity can be obtained with catalytic quantities of strong bases.[17] The presence of electron-releasing (OMe) and -withdrawing (F) groups had little effect on the reaction efficiency (entries 2−5). Substitution at the ortho position of the styrene was tolerated, giving the desired pyrrolidine **4b** in 69% yield (entry 4). Importantly, 6-endo cyclizations of 1,1-disubstituted styrenes to give tosylpiperidine products **7b** and **8b** also proceeded in good yields with complete regiocontrol (entries 7 and 8). We observed that geminal substitution in the backbone was not required for reactivity, and only slight decreases in yield compared with the dimethyl-substituted analogues were observed, although longer reaction times were generally required (cf. entries 3 vs 5 and 7 vs 8). For styrenyl substrates, the major byproduct was the cyclized deprotected product. Reprotection or deprotection of the reaction mixture could easily convert the remainder of the mass balance as desired. The inclusion of a stereocenter next to the amino group (**10a**) gave stereocontrol during the ring-forming event, albeit at a modest level (3:1 dr; entry 10). We were pleased to find that a more geometrically challenging 5-endo cyclization could be achieved with unsaturated amine **11a**, which afforded the fully saturated indole derivative **11b** in 72% yield with 12:1 dr (entry 11). Furthermore, the method is not limited to tosylamines, as the sulfamate proved to be a competent nucleophile, giving access to a unique 6-exo cyclization (entry 12).

From the beginning of our studies, we presumed that the role of the thiophenol was to act as the H-atom donor and that the

Table 2. Scope of the Intramolecular Anti-Markovnikov Hydroamination Reaction of Unsaturated Amines[a]



Entry	Substrate	Product	Time	Yield
				
1	**1a** Ar = C_6H_5, R, R' = Me	**1b**	24h	82%
2	**2a** Ar = 4-(F)C_6H_4, R, R' = Me	**2b**	24h	89%
3	**3a** Ar = 4-(MeO)C_6H_4, R, R' = Me	**3b**	30h	88%
4	**4a** Ar = 2-(MeO)C_6H_4, R, R' = Me	**4b**	40h	69%
5	**5a** Ar = 4-(MeO)C_6H_4, R, R' = H	**5b**	48h	79%
6	**6a** Ar = 4-(MeO)C_6H_4, R = H, R' = *i*-Pr	**6b**	39h	88% 1.6:1 d.r.[b]
				
7	**7a** R = Me	**7b**	48h	79%
8	**8a** R = H	**8b**	96h	60%
				
9	**9a** R = H; R' = Ph	**9b**	96h	70%
10	**10a** R = Me; R' = H	**10b**	96h	56% 3:1 d.r.[b]
				
11	**11a**	**11b**	96h	72% 12:1 d.r.[b]
				
12	**12a**	**12b**	96h	54%

[a]In all cases, the reaction mixture was irradiated with a 15 W, 450 nm LED flood lamp. The reported yields are average isolated yields from two trials. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

subsequent thiyl radical could serve to reoxidize the reduced form of **A**. To exclude alternative mechanistic pathways, we conducted several control experiments. We considered that thiophenol could participate in a thiol−ene reaction catalyzed by the acridinium catalyst,[18] after which nucleophilic displacement of the resultant phenylthioether could furnish the observed products. However, this prospect seemed unlikely because the limited number of examples of this reactivity require either strong exogenous base or elevated temperatures. To probe the potential involvement of this reaction pathway, we prepared Boc-protected unsaturated amine **13** and submitted it to the reaction conditions shown in eq 3. As we observed only unchanged starting material and no incorporation of thiophenol into the molecule, we believe that the thiol−ene pathway likely is not operative in this transformation.

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Conditions: A) (t-BuO)$_2$ (0.5 equiv), PhSH (0.15 equiv), C_6H_6 [0.4 M],140 °C, 96h.
B) AIBN (0.2 equiv), PhSH (0.2 equiv), DCE [0.5 M], 85 °C, 96h.

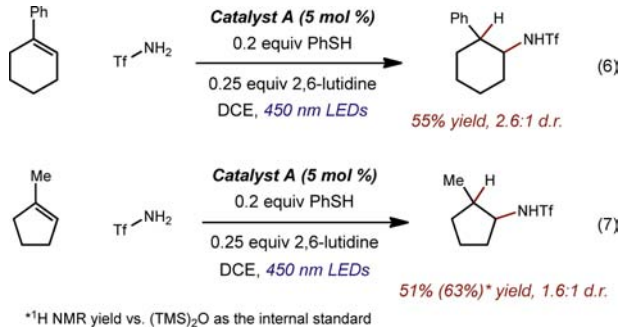
We also considered the possibility that thiophenol could act solely as a hydrogen-atom shuttle.[19] In this context, we submitted isoprenyl amine **9a** to thiophenol with di-*tert*-butyl peroxide or azobis(isobutyronitrile) (AIBN) as a thermal radical initiator (conditions A or B, respectively; eq 4). No reactivity was observed in either case, suggesting that the formation of N-centered radical intermediates was also unlikely.

Finally, the observation of varying quantities of PhSSPh in the crude reaction mixtures led us to question whether this byproduct was active in the catalytic cycle. Subjection of **9a** to reaction conditions employing PhSSPh instead of PhSH afforded the anti-Markovnikov hydroamination product in 55% yield (eq 5). While this observation is not fully understood

at this time, it is conceivable that diphenyl disulfide could serve as a reservoir of phenyl thiyl radical via oxidation of the disulfide (E_p^{ox} = +1.51 V vs SCE)[20] and subsequent fragmentation. It is possible that the phenyl thiyl radical could then act as an oxidant for the reduced form of catalyst **A** in a manner similar to the mechanism invoked in our prior communication.[10]

On the basis of these experiments and the reactivity observed in this study, we have developed the working mechanistic hypothesis depicted in Scheme 1. After oxidation of unsaturated amine **9a** by the excited state of the catalyst (**A***), anti-Markovnikov addition of the amine would furnish intermediate radical cation **14**. H-atom transfer from thiophenol to **14** would furnish the desired amine heterocycle **9b** after proton loss. Thiyl radical **15** formed by reduction of **A*** could serve as a reductant for thiyl radical **16** derived from thiophenol to reset catalyst **A** and generate thiophenoxide anion (**17**). Given the known reduction potential of **16** (E_p^{red} = +0.45 V vs SCE)[21] and the oxidation potential of **15** ($E_{1/2}^{ox}$ = −0.57 V vs SCE),[22] we estimate that this electron transfer should be exergonic. **17** then should serve as a mild base to neutralize the acid generated during the course of the reaction.

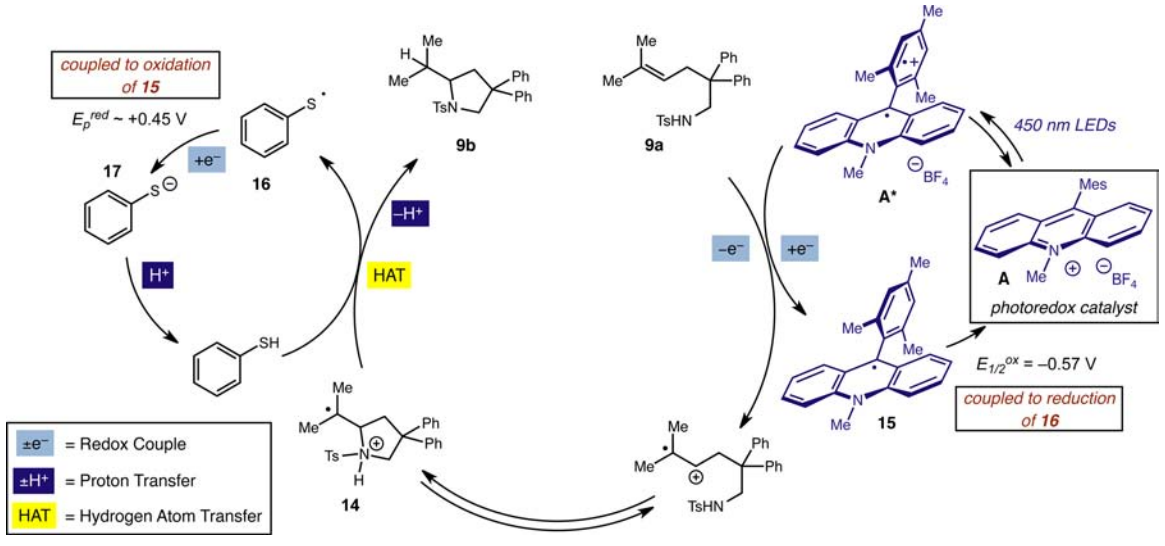
We were pleased to find that this protocol could be extended to include examples of intermolecular alkene hydroamination (eqs 6 and 7). Treatment of styrenyl and alkenyl substrates



with 3.0 equiv of triflylamide under our standard reaction conditions with the addition of 0.25 equiv of 2,6-lutidine gave the desired products in modest yields as single regioisomers. To our knowledge, this represents the first example of an organocatalytic intermolecular anti-Markovnikov alkene hydroamination.

In conclusion, we have reported an intramolecular anti-Markovnikov hydroamination method using catalytic amounts of thiophenol and an organic photocatalyst promoted by visible light. The reaction conditions are mild and effect a range of cyclization modes to give important nitrogen-containing heterocycles. We have also demonstrated that this protocol

Scheme 1. Working Mechanism for Direct Anti-Markovnikov Hydroamination of Alkenes



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can be extended to intermolecular reactions. Efforts to obtain a better understanding of the mechanism of this transformation are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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